Safety of endovascular treatment of carotid artery stenosis compared with surgical treatment: A meta-analysis

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Background and Purpose: **Since publication of previous meta-analyses comparing endovascular and surgical treatment of patients with carotid artery stenosis, two further large-scale trials have been conducted, almost doubling the number of patients available for analysis. Therefore, it is justified to update these meta-analyses.**

Methods: **Relevant trials were identified by a search of the literature using an electronic database. Trials with a nonrandomized patient allocation were not included. We focused on events within 30 days after intervention and made two sets of analysis: one with all trials and one with large trials exclusively including symptomatic patients.**

Results: **Only Endartérectomie Versus Angioplastie chez les patients ayant une Sténose carotide Symptomatique Serrée (EVA3S) and Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) were identified to be included in the updated meta-analysis. In total, 2985 patients were included in eight trials of which 89% were symptomatic. In contrast to previous analyses, this meta-analysis found a significant difference between the odds ratios of any stroke or death within 30 days after treatment with a disadvantage of endovascular treatment when analysing all trials (odds ratio [OR], 1.38; 95% confidence interval [CI] 1.04-1.83; $P = .024$). Significant heterogeneity was found for this analysis ($P = .03$). The increase of the odds of suffering from disabling stroke or death in the endovascular compared with the surgical group was not significant in the analysis of all trials (OR, 1.37; 95% CI, 0.92-2.04; $P = .12$); no heterogeneity was found for this analysis ($P = .27$). In the analysis of the large trials with symptomatic patients, the OR for the endpoint any stroke or death was 1.29 (95% CI 0.94-1.76; $P = .11$); with a hint for heterogeneity ($P = .10$). For the endpoint disabling stroke or death, the OR was 1.33 (95% CI 0.89-1.93; $P = .17$) without any heterogeneity ($P = .58$).**

Conclusion: **The expressiveness of this meta-analysis is limited by the heterogeneity of some tests. The main result is that surgical treatment still remains the gold standard for treatment of patients with symptomatic carotid artery stenosis, who do not have an increased surgical risk. Carotid artery stenting is neither safer than nor as safe as carotid endarterectomy in large clinical trials when short-term stroke and death rates are taken into account. Further recruitment into ongoing randomized trials is strongly recommended. (J Vasc Surg 2008;47:350-5.)**

Safety and efficacy of endovascular treatment in comparison with carotid endarterectomy in patients with either symptomatic or asymptomatic severe carotid artery stenosis is still a matter of ongoing debate. Two meta-analyses on this subject were published in 2005, analyzing six randomized trials.[1,2] In the meantime, two more large-scale trials exclusively including patients with symptomatic carotid artery stenosis have been published, almost doubling the number of patients available for analysis.[3,4] Therefore, we thought it would be important to update the recently published meta-analyses, focusing in particular on patients with symptomatic stenosis. Because limited long-term follow-up data of these two trials are available or have been published with respect to the older trials, we limited the present meta-analysis to safety concerns.

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Competition of interest: none.

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MATERIAL AND METHODS

Relevant trials were identified by a search of the literature using an electronic database (PubMed). Search terms included the phrases carotid arteries, stenosis, endovascular, stenting, angioplasty, endarterectomy, and randomized in various combinations. The search was limited to publications between October 2004 and March 2007. Randomized trials comparing carotid endovascular treatment with carotid endarterectomy in patients of any age or sex with carotid artery stenosis were included. Trials with a nonrandomized patient allocation were excluded.

For each study, data were sifted out regarding randomization, number of patients allocated to each treatment modality, and the outcome following an intention-to-treat principle, number of patients treated within the allocated treatment arm, intervention characteristics, and outcome

measures, such as stroke of any severity or death within 30 days after procedure. Strokes were classified, if possible, as disabling or not, based on the method used by the authors of the original publication. Data from earlier trials (prior to October 2004) were extracted from the previous meta-analyses and verified using the original publication by two of the authors (PR, HHE). The analysis was restricted to 30-day events because we were aware that only few relevant long-term data have been published. In addition, no analyses of cardiovascular events or local complications (eg, nerve palsy) have been done because these have not been reported from the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial so far.

Two sets of trials were used for a meta-analysis. First, all identified trials were combined to be consistent with previous publications. Second, only trials with more than 200 patients, at least nearly exclusive inclusion (>95%) of patients with symptomatic stenosis and peer-reviewed publication were combined.

Results of the meta-analysis were reported as odds ratios (OR), (the odds of an unfavorable outcome among patients treated by endovascular intervention compared with the corresponding odds among patients treated surgically) and were calculated using the Peto fixed-effect method. This method was used to be consistent with the previous published meta-analyses. Heterogeneity was assessed using Cochran Q statistic, and *P* values obtained by comparing the statistic with a χ^2 distribution with k-1 degrees of freedom, where k is the number of studies. We also used the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance and is calculated as 100% x (Q-df)/Q where Q is the Cochran Q statistic.[5] I^2 is an intuitive and simple expression of the inconsistency of studies' results because, unlike Q, it does not inherently depend upon the number of studies considered. For all analyses StatsDirect statistical software version 2.5.6 was used.

RESULTS

In addition to the trials analyzed by Coward and Qureshi (Leicester,[6] WALLSTENT,[7] CAVATAS,[8] Kentucky-A[9] and –B,[10] SAPPHIRE[11]) only EVA3S and SPACE fulfilled our criteria and were included in the updated meta-analysis. Another large-scale trial (CaRESS) was excluded because of the nonrandomized treatment allocation.[12] Another small trial included in the meta-analysis of Qureshi[2] was not included in our study because the published results were incomplete. Twenty-three patients were randomized into this trial, 30-day follow-up data of only 13 of these patients were reported.[13] In total, 2985 patients were enrolled in these eight trials of which 2646 (89%) were symptomatic. Five of the eight trials included only patients with symptomatic carotid artery stenosis, one of them is not peer reviewed published,[7] and two of them were small.[9,10] The majority (71%) of the SAPPHIRE-population were asymptomatic patients. Baseline data or results for the subgroup of symptomatic patients could not be extracted from the original publication or subsequent publications.[11] Therefore, this trial was not included in the second meta-analysis. In contrast, CAVATAS was included into the second analysis because only 16 (3.2%) of the patients were asymptomatic. In total, only three trials remained for the second meta-analysis.

A summary of the trials published before 2005 is not presented here; this can be found in the work of Coward et al.[1]

EVA3S. The Endartérectomie Versus Angioplastie chez les patients ayant une Sténose carotide Symptomatique Serrée (EVA3S) was a French multicenter, noninferiority randomized trial with national research organization funding.[4] Patients were eligible if they had experienced a carotid transient ischemic attack (TIA) or nondisabling stroke within 4 months before randomization, associated with an atherosclerotic stenosis within the ipsilateral carotid bifurcation of at least 60%$^{\text{NASCET}}$, which investigators believe was suitable for both carotid surgery and angioplasty. The primary endpoint was any stroke or death within 30 days of the procedure. In EVA3S, the interventionalists had to document at least 12 cases of carotid artery stenting (CAS) or at least five cases of CAS and 30 cases of endovascular treatment of other supra-aortic trunks.[14] Since February 2003, the use of a emboli protection device (EPD) was mandatory. A total of 92% of the EVA3S-CAS-patients were treated with an EPD.[15] In September 2005, recruitment into EVA-3S was stopped by the data safety and monitoring board after enrolling 527 patients. A total of 265 patients were randomized into the CAS and 262 into the CEA group. Seven patients, who did not undergo carotid repair, were excluded from the intention to treat (ITT) analysis of the risk of any stroke or death within 30 days after treatment. Primary outcome events occurred in 25 (9.6%) patients of the CAS and in 10 (3.9%) of the CEA group. This reflects an odds ratio of 2.5 (95% confidence interval [CI] 1.2-5.1; $P = .01$) for an increased periprocedural risk in the CAS group. Disabling strokes or death occurred in nine (3.4%) patients of the CAS and four (1.5%) patients of the CEA group.

SPACE. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial investigated whether CAS is not inferior to CEA in the treatment of severe symptomatic carotid artery stenosis.[3] The trial was done in Germany, Austria, and Switzerland. Patients over the age of 50 years with symptomatic (transient ischemic attack or minor stroke) stenosis (at least 70%$^{\text{ECST}}$) eligible for both methods could be recruited into this trial. Primary endpoint of SPACE was the rate of ipsilateral stroke or death between randomization and day 30 after treatment. The 30-day rate of any stroke or death was not a prespecified endpoint, but can easily calculate from other endpoint data. In SPACE, the primary interventionalist of each center had to demonstrate 25 successful interventions prior to participation in the trial, whereas secondary investigators got a preliminary certificate after 10 interventions. A second interim analysis based on 1200 patients revealed primary event rates of 6.84% in the CAS

Table. Rates of outcome events at 30 days from the randomized trials comparing endovascular with surgical treatment in patients with severe carotid artery stenosis (ITT data)

	30-day stroke or death		*30-day disabling stroke or death*	
Outcome	*CAS - no (%)*	*CEA - no (%)*	*CAS - no (%)*	*CEA - no (%)*
Leicester[6]	5 (45.5)	0 (0)	3 (27.3)	0 (0)
WALLSTENT[7]	13 (12.1)	5 (4.5)	unknown	unknown
CAVATAS[8]	25 (10.0)	25 (9.9)	16 (6.4)	15 (5.9)
Kentucky-A[9]	0 (0)	1 (2.0)	0 (0)	1 (2.2)
Kentucky-B[10]	0 (0)	0 (0)	0 (0)	0 (0)
SAPPHIRE[11]	8 (4.8)	9 (5.4)	unknown	unknown
EVA3S[4]	25 (9.6)	10 (3.9)	9 (3.4)	4 (1.5)
SPACE	45 (7.4)	39 (6.6)	31 (5.1)	23 (3.9)

ITT, Intention to treat; *CAS,* carotid artery stenting; *CEA,* carotid endarterectomy.

und 6.34% in the CEA-group. An updated sample-size calculation found that 2500 patients would be necessary to proof the noninferiority of CAS with a power of 80%.[3] Therefore, randomization was stopped after 1214 patients. In this entire population, the rate of ipsilateral stroke or death was 6.92% in the 607 patients of the CAS and 6.45% in the 589 patients of the CEA group. The upper limit of the 95% confidence interval (CI) of the absolute risk reduction was 2.87 and, thus, exceeded the predefined noninferiority margin of 2.5%. Therefore, SPACE failed to prove the noninferiority of CAS compared with CEA in treating patients with symptomatic carotid artery stenosis. The rate of any stroke or death within 30 days was 7.4% in the CAS and 6.6% in the CEA group. The rate of disabling stroke or death was 5.1% in the CAS and 3.9% in the CEA group. In SPACE, the use of an EPD was left to the discretion of an investigator; finally, 27% of the SPACE-CAS population was treated with an EPD.

The eight trials differ significantly regarding the study population and technical details. SAPPHIRE attempted to include only patients considered to be at high surgical risk for CEA. In three trials, diagnostic angiography was mandatory before randomization and therefore, its risk added to the treatment. In the other five trials, patients could be randomized according to the results of noninvasive techniques, mainly duplex ultrasound. In CAVATAS, the majority of the patients were treated by angioplasty alone: only 26% were treated using a stent. Use of an EPD was mandatory in SAPPHIRE and in a predominant number of patients in EVA3S. In SPACE, it was left to the investigators' discretion whether to use an EPD. Slight differences were also present in terms of stroke definition: SPACE and EVA3S counted all events lasting longer than 24 hours, whereas some other trials used a 7-day time interval. The outcome as a composite of any stroke or death within 30 days after procedure was available for all eight trials. Data on disabling strokes were available for six trials. Disability was defined as a score of at least 3 on the modified Rankin Scale (mRS) in EVA3S and SPACE. CAVATAS defined disability as requiring help from another person for more than 30 days, which is roughly equivalent to a score of 3 or above on the mRS. The table shows the rates of outcome events for each of the studies.

Meta-analysis of all studies shows a significant 38% increase in the odds of suffering any stroke or death within 30 days after treatment in the endovascular treatment group compared with the surgical group (OR, 1.38; 95% CI 1.04-1.83; $P = .024$). A significant heterogeneity was found (Cochran Q = 14.0; $P = .03$) with an I^2 of 57.1% (Fig 1, *a*). After exclusion of non-peer-reviewed and small trials and those with a majority of asymptomatic patients, the combined OR is somewhat smaller (1.29) and the 1 is included within the 95% confidence interval (95% CI 0.94-1.76; $P = .11$). No significant heterogeneity was found for this analysis (Cochran Q = 4.5; $P = .10$). However, an I^2 value of 55.9% is still regarded as substantial heterogeneity (Fig 2, *a*).[16]

Combining all trials, there was a nonsignificant 37% increase of the odds of suffering disabling stroke or death after treatment in the endovascular treatment group compared with the surgical group (OR, 1.37; 95% CI, 0.92-2.04; $P = .12$). No significant heterogeneity was found for this analysis (Cochran Q = 5.2; $P = .27$) with a substantially low value of I^2 (22.8%) (Fig 1, *b*). In the analysis of the large trials with symptomatic patients, we obtained a combined OR very close to the previous one (1.33; 95% CI 0.89-1.93; $P = .17$); no significant heterogeneity was found (Cochran Q = 1.1; $P = .58$) with an I^2 value of 0% (Fig 2, *b*).

DISCUSSION

It has long been established that carotid endarterectomy can prevent further strokes after a cerebrovascular event has been caused by severe carotid artery stenosis. A combined analysis of the data from three major randomized trials found a 30-day rate of any stroke or death of 8.4% in patients with moderate (50%-69%^{NASCET}) and of 6.2% in patients with severe (70%-99%^{NASCET}) carotid artery stenosis.[17] Carotid artery stenting has been increasingly used for treatment of patients with carotid artery stenosis, despite the lack of evidence from large-scale randomized trials of equivalent periprocedural risk and efficacy. Two major trials have been published in 2006.[3,4] One found no significant differences with regard to periprocedural risk between the two treatment modalities, but missed the primary aim of proving that CAS was not inferior.[3] The other trial found a significantly increased risk for CAS.[4]

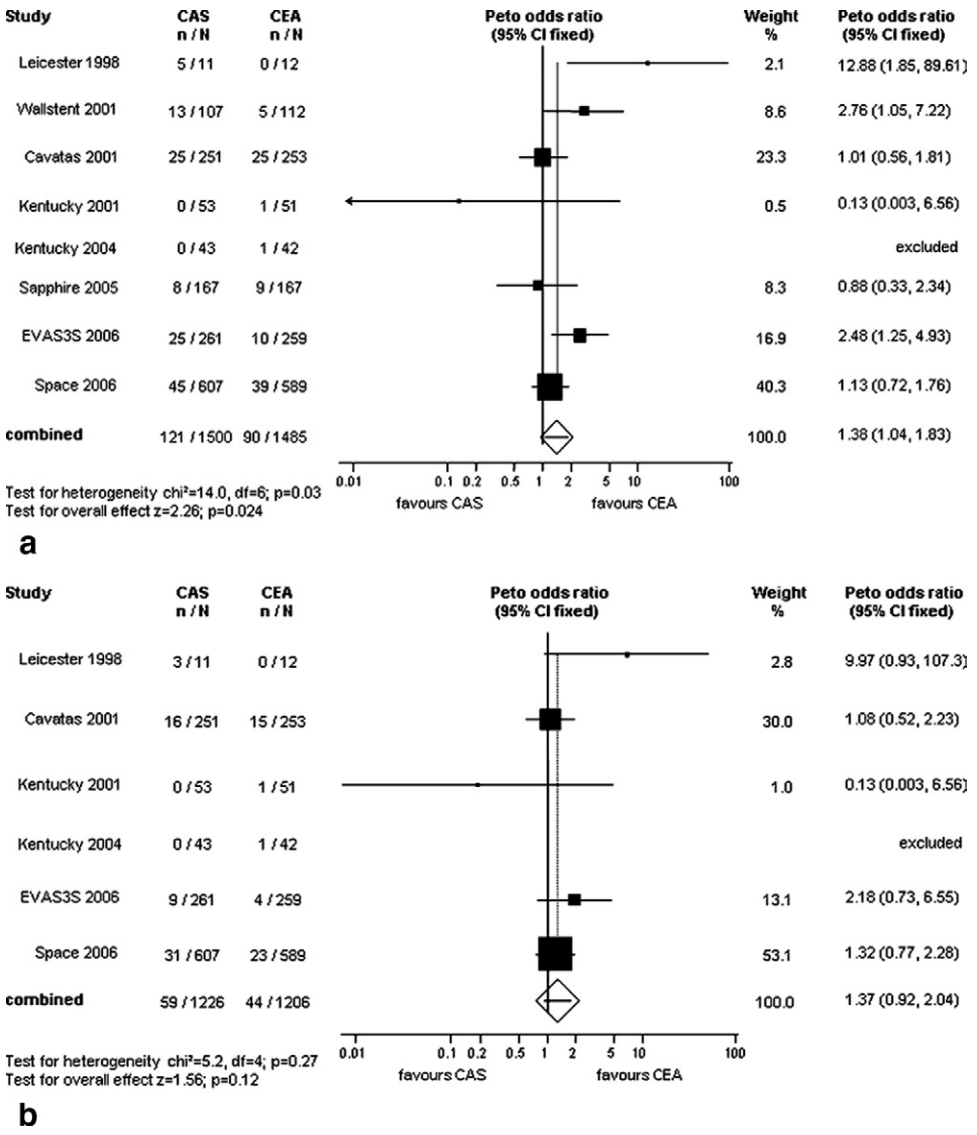

Fig 1. Effect of endovascular vs surgical treatment for patients with severe carotid artery stenosis from all randomized trials on the combined endpoint (**a**) any stroke or death within 30 days and (**b**) disabling stroke or death within 30 days.

It is the strength of this meta-analysis that the case number was doubled compared with the previous ones. In addition, we were able to include the entire SPACE-cohort in this analysis and not only the cohort of the second interim analysis, which has been published so far. After inclusion of these two trials in the meta-analysis of all available randomized trials, a significantly increased periprocedural risk for the endovascular treatment regarding any stroke or death compared with the surgical treatment can be demonstrated. But for this endpoint, significant heterogeneity was found between the trials, limiting the expressiveness of this analysis. A meta-analysis using a random model, revealed a nonsignificant trend towards surgery (OR 1.46; 95% CI 0.9-2.35). Therefore, this result has to be interpreted with caution.

Possible reasons for the heterogeneity are the facts that some trials also included asymptomatic patients, that the endovascular technique changed during the time, and that the operator experience was different between the trials. These differences were the main reason to perform also a meta-analysis focused on the large trials with symptomatic patients. Beside the two recent trials, we included only CAVATAS into this analysis because the other trials did not report the results of the symptomatic subgroup,[11] were not peer-reviewed,[7] or included only few patients.[9] This analysis found a nonsignificant difference in favor of the surgical therapy. We did not focus on the analysis of different interventional techniques and, therefore, added also CAVATAS into this analysis despite different endovascular techniques; CAVATAS predominantly used balloon angioplasty alone, whereas the later tended to use stenting with cerebral protection. Nevertheless, no heterogeneity was found for this analysis. Also, the prerequisites for the investigators seemed to have

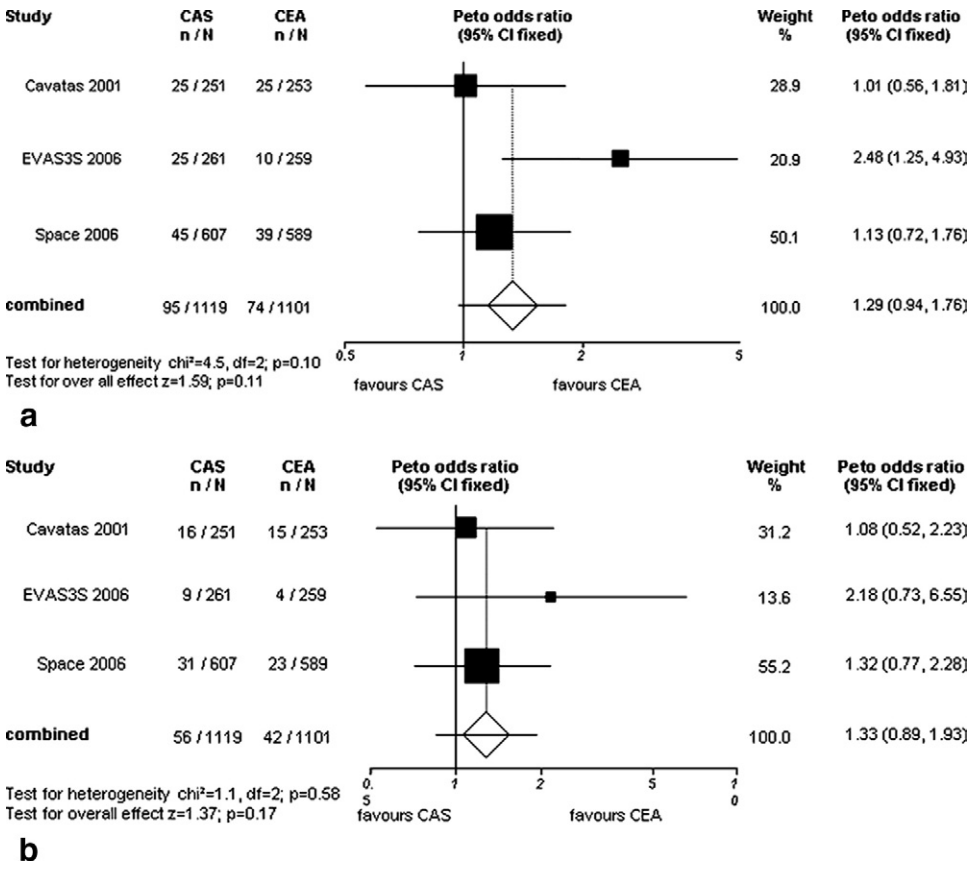

Fig 2. Effect of endovascular vs surgical treatment for patients with severe symptomatic carotid artery stenosis from randomized, peer-reviewed published trials on the combined endpoint (**a**) any stroke or death within 30 days and (**b**) disabling stroke or death within 30 days.

only a limited effect for the different results of these trials. For instance, in EVA3S, the periprocedural complication rate was not different between experienced and inexperienced physicians.[18] This was also observed in the recently published CAPTURE registry.[19] This registry included 3500 patients with high surgical risk, comparable with the SAPPHIRE criteria. All patients were examined within 14 days prior to treatment by an independent neurologist. The neurologist examination was repeated at 24 hours and at 30 days after procedure. The overall complication rate, expressed as the rate of composite of death, any stroke, or myocardial infarction within 30 days postprocedure was 6.3% It is remarkable that most patients were asymptomatic (n = 3018) with a complication rate of 5.4%; for symptomatic patients (n = 482) the complication rate was 12.0%. In SAPPHIRE, which was the rationale for this post approval registry, this rate had been 2.1% in the symptomatic subgroup.[11] It should be mentioned that based on level Ia evidence acceptable complication rates are 3.0% for asymptomatic and 6.0% for symptomatic patients.[20,21] In CAPTURE, three different levels of operator experiences were defined with almost no statistical differences in outcomes by physician levels in all patients or in the subgroups of asymptomatic patients. In symptomatic patients, there was a trend towards better results with higher level of experience (4.2% vs 12.4%), but only 48 patients were treated by highly experienced operators, therefore the confidence interval is broad and this difference also is not significant.

Another argument for the less important influence of the technique or the operator experience for the periprocedural risk are the comparable complication rates in the CAS groups of these three trials: 10.0% in CAVATAS, 9.6% in EVA3S, and 7.7% in SPACE for any stroke or death. Thus, the differences between CAVATAS, EVA3S, and SPACE can hardly be explained with differences in the endovascular arms. It is more important that there were relevant differences within the surgical arms. Despite the long experience of surgeons with carotid endarterectomy in any trial, almost a threefold difference between the surgical complications rates can be observed: 3.9%, 6.5%, and 9.9% in EVA3S, SPACE, and CAVATAS, respectively. The reasons for these differences are still under discussion.

Another reason for the heterogeneity between the trials is the early data-dependent stop of EVA3S. Such "early stopped trials" are at risk of over-estimating the risk or benefit of the treatment.

On the other hand, for the endpoint disabling stroke or death, there was no statistically significant difference between the two treatment modalities in both analyses. However, the power of the comparison was low with only 100 events in six trials providing information about stroke severity. Nevertheless, the size of the effect was comparable (one third increase in relative risk) with that observed with the endpoint any stroke or death, and no heterogeneity was observed.

CONCLUSIONS

Based on the significant heterogeneity of the overall meta-analysis and the nonsignificant differences in the other analyses, the main result of this analysis is that surgical treatment is still the gold standard for treatment of patients with symptomatic carotid artery stenosis, who do not have an increased surgical risk.

According to present knowledge, CAS has not yet been shown to be as safe as or even safer than carotid endarterectomy in large clinical trials when considering short-term stroke and death rates. To increase the knowledge about the role of CAS in treating patients with carotid artery stenosis, further recruitment into ongoing randomized trials is strongly recommended.

The authors are members of the steering and writing committees of the trials included in this analysis (SPACE: PR, WH, HHE; EVA3S: JLM, GC) and investigators of EVA3S (JPF, JMB).

AUTHOR CONTRIBUTIONS

Conception and design: PR, WH, JM, HE
Analysis and interpretation: PR, HE, GC
Data collection: PR, GC, WH, JF, JB, HE, JM
Writing the article: PR, WH, HE, JM
Critical revision of the article: WH, HE, JM, JB, JF
Final approval of the article: WH, HE, JM, JF, JB
Statistical analysis: PR, GC
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Overall responsibility: JM

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